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The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report—2011

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The Registry of the International Society for Heart and Lung Transplantation (ISHLT) has documented trends in clinical lung and heart-lung transplantation since the inception of these procedures. Detailed heart-lung transplantation data have been included in the Registry annual reports since 1984 and lung transplantation data since 1989. Through June 30, 2010, the Registry contains data on 4,248 heart-lung and 38,119 lung transplants from centers around the world. This 28th Lung and Heart-Lung Registry Report summarizes the current status of lung and heart-lung transplantation by reporting data on this international group of patients, focusing on adults. More detailed information is presented in the full set of more than 200 slides that can be found on the ISHLT Web site at www.ishlt.org/registries/.

Statistical methods

Survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test; survival graphs were truncated when the remaining number of recipients was < 10. Multivariable analyses were performed using Cox proportional hazards models. The results of the multivariable analyses are reported as relative risks (RR) with a corresponding 95% confidence interval or p-value. A RR > 1.0 indicates that the factor was associated with a higher probability of the event; conversely, a RR < 1.0 means the factor was linked to a lower likelihood of the event. Where appropriate, a more detailed explanation about the analytic methodology accompanies the slides (in the "Notes Page" view), which are accessible at www.ishlt.org/registries/.

Multiple imputation was used to handle missing information for continuous data fields such as ischemic time and donor age.[1] This method produces an estimated value for the missing value based on the other characteristics of the patient, donor, and/or transplant. The algorithm is performed multiple times, producing new estimates for the missing information. Models are fit on each imputed data set and then combined to produce a final set of estimates from which the RR estimates and p-values are obtained.

Lung transplantation

Centers and activity

The total of 3,272 lung transplantation procedures reported to the Registry in 2009 was the highest of any year to date (Figure 1). Overall, the yearly growth in reported procedures has been steady since 2000. This is a result of increased transplants from long-time Registry contributors and the continued addition of transplants from centers and countries not previously reporting. As in prior Registry reports, the increased procedure numbers have largely been the result of consistent growth in the number of bilateral transplants, with the number of single-lung transplants remaining largely consistent since the mid-1990s.

Since January 1, 2000, 174 centers reported to the Registry, with data from 16 centers newly added to the Registry in the last year (Figure 2). Data compiled between January 2000 and June 2010 show that 50% of the transplant procedures were performed at 30 centers with an average activity of 30 or more transplants per year. The 7 centers with an average activity of 50 or more transplants performed 20% of procedures reported world-

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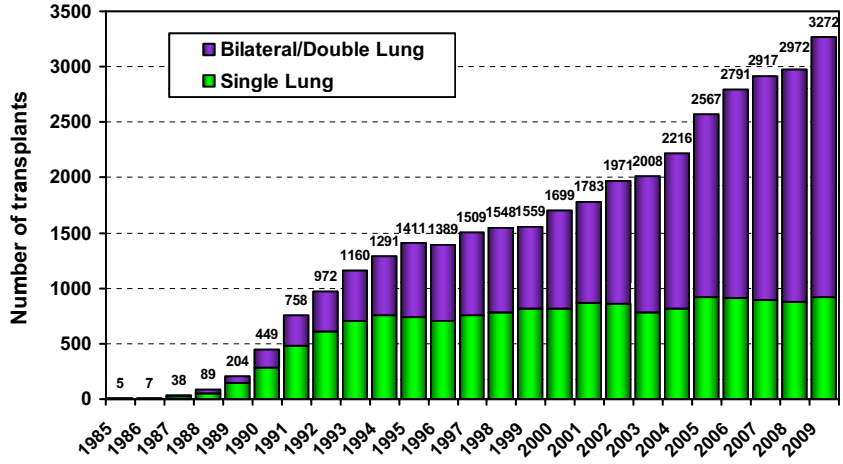

Figure 1 Number of lung transplant procedures reported by year and procedure type. This figure includes transplants reported to the International Society for Heart and Lung Transplantation (ISHLT) Registry from organ exchange organizations in countries with a data-sharing agreement and also transplants reported by individual centers in countries without a specific data-sharing agreement between ISHLT and the national transplant organization. Therefore, this figure may not fully represent the total number of procedures worldwide.

wide during this period. In contrast, 82 centers (47%) averaged fewer than 10 transplants per year, accounting for 9% of total transplant volume during this interval.

Donor and recipient age

The median age of lung donors in the first 6 months of 2010 averaged 37.0 years, a 2-year reduction compared with a peak average age of 39 years in 2009. The percentage of donors aged 50 to 59 years and older than 59 years has increased during the past 20 years but has remained essentially constant since 2005 (Figure 3). The median age of recipients appears to have hit a plateau as well, with an unchanged median of 55 years in the first 6 months of 2010 (Figure 4). In the first 6 months of 2010, the number of aged older than 65. Specifically, 28 transplant procedures were reported in those aged 66 or older (1.6%) in 2000, compared with 182 in the first 6 months of 2010 (12.1%). The greatest proportion of adult lung transplant procedures in recipients aged 60 and older were performed in North America (see supplemental slides at www.ishlt.org/registries/).

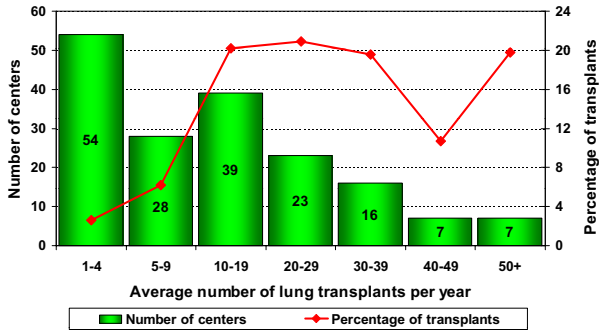

Figure 2 Distribution of lung transplants by center volume, January 2000 through June 2010. The bars indicate number of centers and the line graph indicates percentage of total transplants by center volume.

Indications and procedure types

Major indications for adult lung transplantation between January 1995 and June 2010 are listed in Table 1. Most procedures during this period were performed for chronic obstructive pulmonary disease (COPD), exclusive of α_1-antitrypsin (AAT)–deficiency emphysema in 35%, followed by idiopathic pulmonary fibrosis (IPF) in 23%, cystic fibrosis (CF) in 17%, and AAT in 6%. Transplant procedures for IPF have steadily increased during the past decade, from 16% of all procedures performed in 2000 to 28% in 2009, approaching the proportion reported for non-AAT COPD (30%) performed that year (Figure 5).

Since 1996, the proportion of bilateral transplant procedures in adult recipients has risen overall for each of the 4 major indications (Figure 6). Excluded from the figure is CF, in which bilateral transplant is nearly uniform. In all age groups combined and across all diagnoses, bilateral transplantation accounted for 72% of transplant procedures in 2009, the highest proportion of any year (Figure 1).

Acute rejection

Standard reports of acute rejection to the Registry were modified in July 2004 to include the designation of whether the episode was treated or not. Between July 2004 and June 2010, at least 1 episode of acute rejection within the first year was reported in 35% of adult lung recipients, with 89% of these being treated (Figure 7). More rejection episodes (38%) were reported in the youngest adult age category (age 18–34 years) than in older age categories, although these results are not adjusted for diagnosis category or other potential confounding variables. There were no differences in reported acute rejection episodes between men and women. As in prior years, acute rejection rates are categorized by use of induction therapy and maintenance immunosuppression regimen.

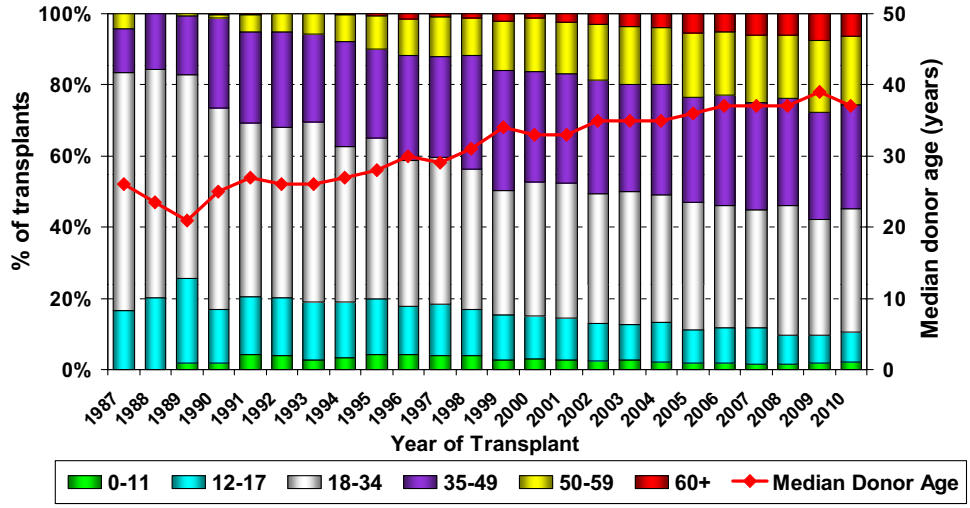

Figure 3 Age distribution of donors of lung transplants by year of transplantation, January 1987 through June 2010. The bars represent categories of ages, and the line represents mean age.

Immunosuppression

Data reported between 2000 and 2009 show that the use of any type of induction therapy increased by approximately 10 percentage points between 2006 and 2007, but has leveled off at about 60% of reported procedures in adult recipients during the past 3 years (Figure 8). There appears to be no consensus regarding use or choice of induction therapy according to the Registry data, despite an increase in the use of interleukin-2 receptor (IL-2R) antagonists and alemtuzumab during the past decade.

Overall survival conditional on living for 14 days after transplantation, according to use of induction therapy, is displayed in Figure 9. Induction therapy appeared to have a favorable effect on survival, based on reported transplants between January 2000 and June 2009. When data from earlier eras is included in survival analyses, these same findings are apparent (see additional slides available at www.ishlt.org/registries). However, these findings should be interpreted with caution because they are not adjusted for age, diagnosis category, center, or other potentially confounding factors.

Follow-up data between July 2004 and June 2010 show induction therapy with an IL-2R antagonist was associated with a lower reported incidence of acute rejection during the first year after transplantation compared with all other induction strategies (Figure 10). The lower rejection rates for IL-2R antagonist use appeared to be similar across age groups, despite apparent differences in rejection rates with other induction strategies by recipient age category (Figure 11).

As in prior reports, there appears to be no consensus maintenance immunosuppressive regimen at 1 year or 5 years. Figure 12 presents a snapshot view of combinations of maintenance immunosuppressive drugs reported at 1 and 5 years according to data compiled between January 2002 and June 2010. Of note, this snapshot view presents different individuals in each group; therefore, immunosuppres-

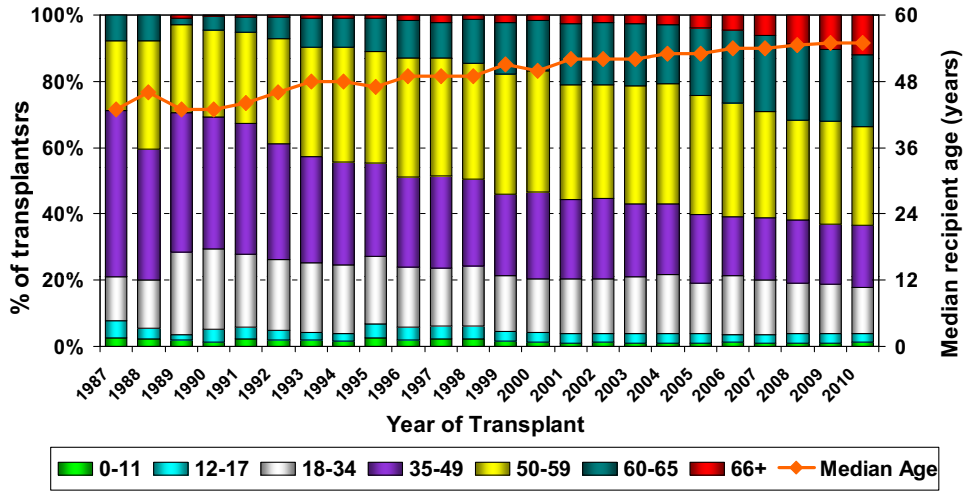

Figure 4 Age distribution of lung recipients by year of transplantation, January 1987 through June 2010. The bars represent categories of ages, and the line represents mean age.

Table 1 Indications for Adult Lung Transplants Performed From January 1995 Through June 2010

Diagnosis	Lung transplant type, No. (%)		
	Single (n = 12,339)	Bilateral/double (n = 18,334)	Total (N = 30,673)
COPD/emphysema	5,769 (46.8)	4,839 (26.4)	10,608 (34.6)
Idiopathic pulmonary fibrosis	3,995 (32.4)	2,938 (16.0)	6,933 (22.6)
Cystic fibrosis	214 (1.7)	4,941 (26.9)	5,155 (16.8)
α1-Antitrypsin–deficiency emphysema	728 (5.9)	1,225 (6.7)	1,953 (6.4)
IPAH	78 (0.6)	894 (4.9)	972 (3.2)
Pulmonary fibrosis, other	424 (3.4)	537 (2.9)	961 (3.1)
Bronchiectasis	50 (0.4)	815 (4.4)	865 (2.8)
Sarcoidosis	236 (1.9)	547 (3.0)	783 (2.6)
Retransplant			
Obliterative bronchiolitis	253 (2.1)	219 (1.2)	472 (1.5)
Not obliterative bronchiolitis	127 (1.0)	162 (0.9)	289 (0.9)
Connective tissue disease	127 (1.0)	232 (1.3)	359 (1.2)
Obliterative bronchiolitis (not retransplant)	80 (0.6)	237 (1.3)	317 (1.0)
Lymphangioleiomyomatosis	101 (0.8)	207 (1.1)	308 (1.0)
Congenital heart disease	43 (0.3)	224 (1.2)	267 (0.9)
Cancer	6 (0.0)	26 (0.1)	32 (0.1)
Other	108 (0.9)	291 (1.6)	399 (1.3)

COPD, chronic obstructive pulmonary disease; IPAH, Idiopathic pulmonary arterial hypertension.

sion trends are not examined within individuals. Tacrolimus was the most frequently used calcineurin inhibitor at 1 year (82%) and 5 years (75%). Mycophenolic acid was the most reported purine synthesis antagonist at both points. The use of sirolimus in combination with other agents was used in 18% of patients at 5 years compared with 8% at 1 year.

The percentage of recipients with reported acute rejection within the first year was highest with cyclosporine-based regimens and lowest with tacrolimus-based regimens according to follow-up assessments performed between July 1, 2004, and June 30, 2010 (Figure 13). As in prior reports, the highest rejection rates were reported for the combination of cyclosporine and azathioprine therapy. However, similar to the induction data, these data are not adjusted for potential confounding variables, such as predisposing diagnosis or age, and acute rejection rates may differ by age group (see additional slides at www.ishlt.org/registries/).

Survival

The overall median survival (or "half-life") for adult lung recipients was 5.5 years according to data compiled between January 1994 and June 2010 (Figure 14), which is longer than the half-life reported in last year's report.[2] Conditional on survival of at least 1 year, the half-life was 7.8 years, which was also slightly increased from last year's report. The unadjusted benchmark survival rate was 88% at 3 months, 79% at 1 year, 64% at 3 years, 53% at 5 years, and 30% at 10 years, all of which are the same as or slightly greater than previously reported.[2]

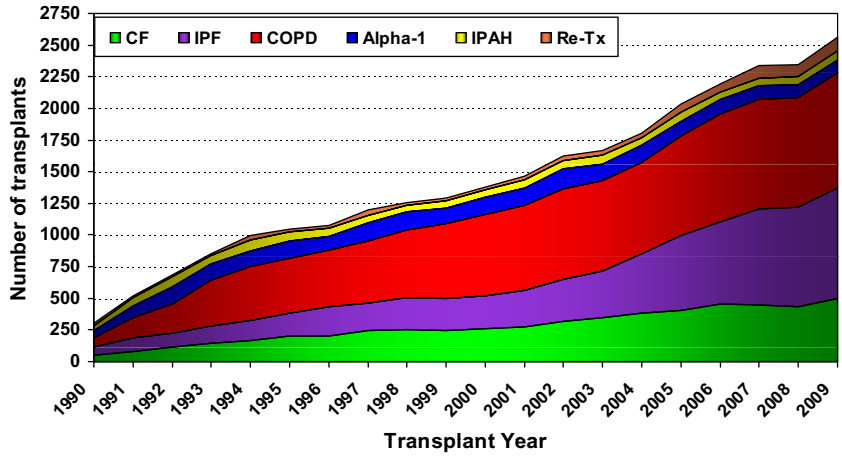

Figure 5 Major indications for adult lung transplants by year. AT Def, α1-antitrypsin–deficiency emphysema; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis.

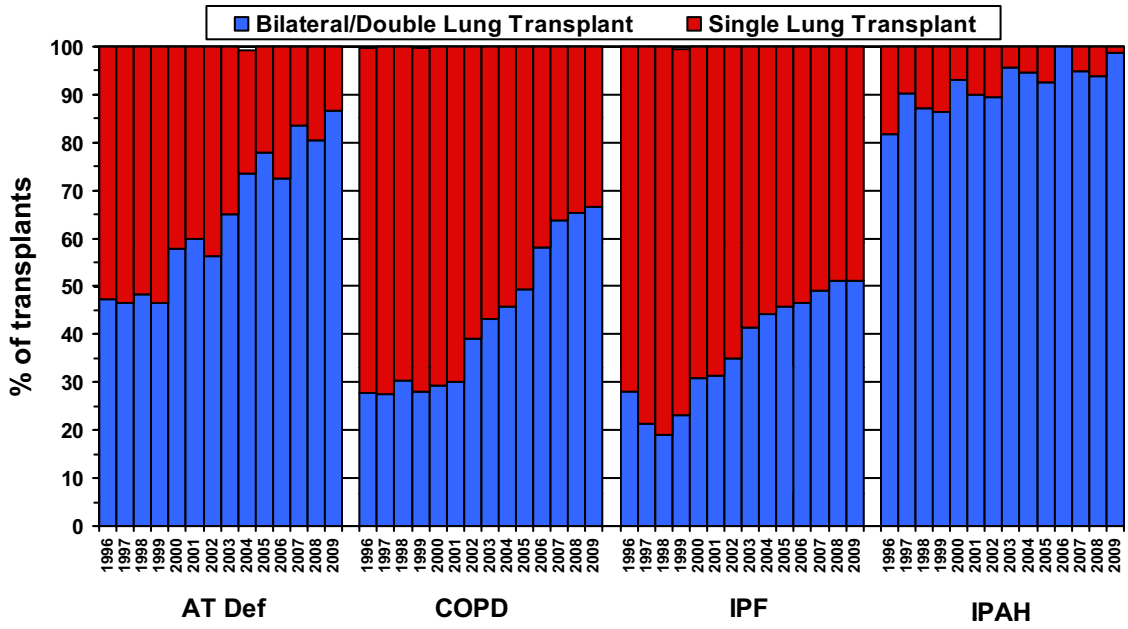

Figure 6 Adult lung transplantation procedure types according to indication and year of transplantation. AT Def, α1-antitrypsin–deficiency emphysema; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis.

Survival rates for single and bilateral transplant recipients were again different (Figure 14). However, as in prior reports, these data should be interpreted with caution, because differences in survival according to procedure type are influenced by clinical factors that inform the decision to perform a particular procedure, including age, underlying diagnosis, recipient comorbidities, preference of the transplant center, and characteristics of the donor lungs.

Overall survival for adult recipients has consistently improved by era, as documented by follow-up data for transplants performed between 1988 and June 2009 (Figure 15). As has been observed in the past, the improved survival in the most current era is largely driven by better early survival: 3-month survival has improved from 82% to 89%, and 1-year survival has improved from 72% to 81%. Compared with the era beginning in 1988, the overall transplant half-life has shown greater improvement (4.7, 4.8, and 5.9 years) than the half-life conditional on 1-year survival (7.9, 7.5, and 8.0 years).

Survival rates are again reported to differ by recipient age according to data compiled between January 1990 and June 2009 (Figure 16). Age groups 50 years and older report

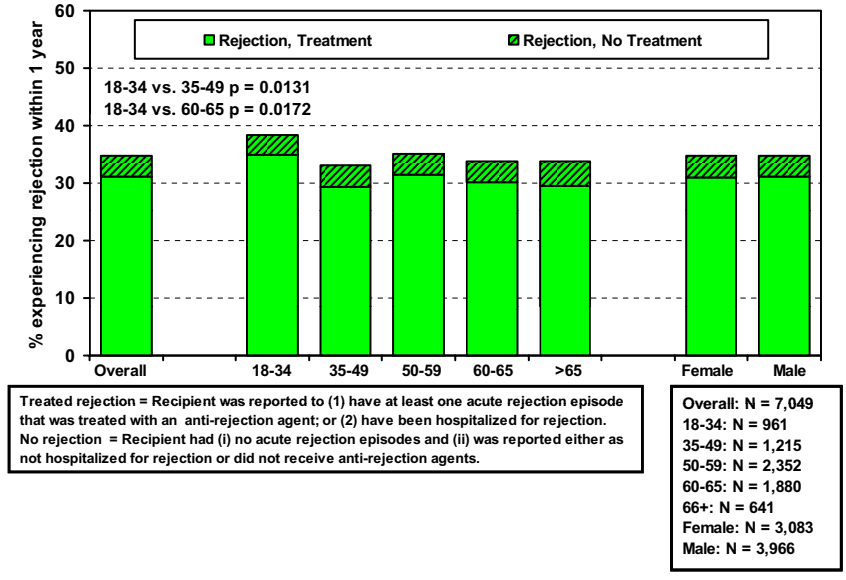

Figure 7 Percentage of adult lung transplant recipients experiencing rejection between hospital discharge and 1 year, by age category and sex. Data presented are based on follow-up reports between July 1, 2004, and June 30, 2010. Analysis is limited to patients who were alive at the time of the discharge.

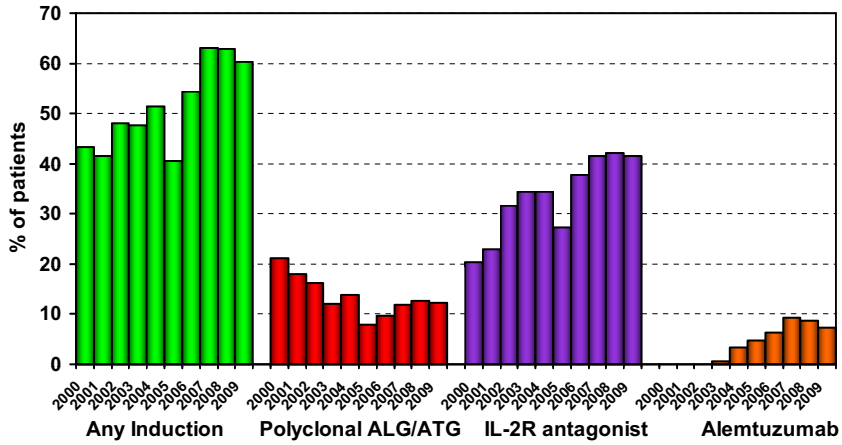

Figure 8 Use of induction immunosuppression by year of transplant in adult lung recipients. ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; IL-2R, interleukin-2 receptor. Analysis is limited to patients receiving prednisone and who were alive at the time of the discharge.

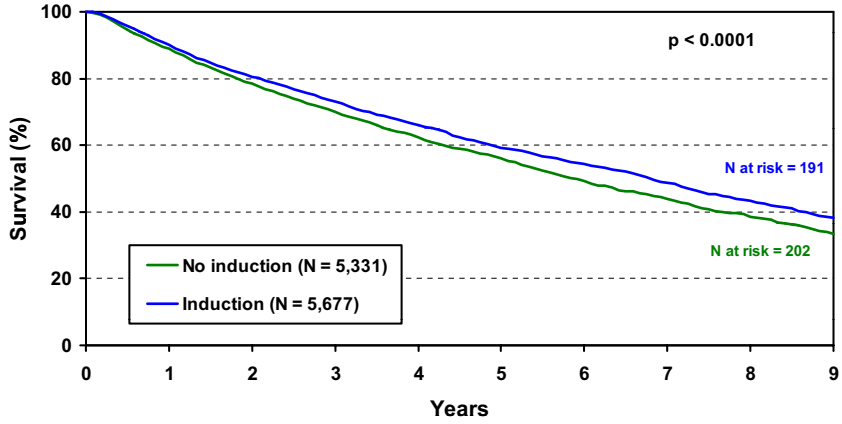

Figure 9 Kaplan-Meier survival after adult lung transplantation for transplants performed from January 2000 through June 2009, stratified by induction usage. Data presented are conditional on survival to 14 days.

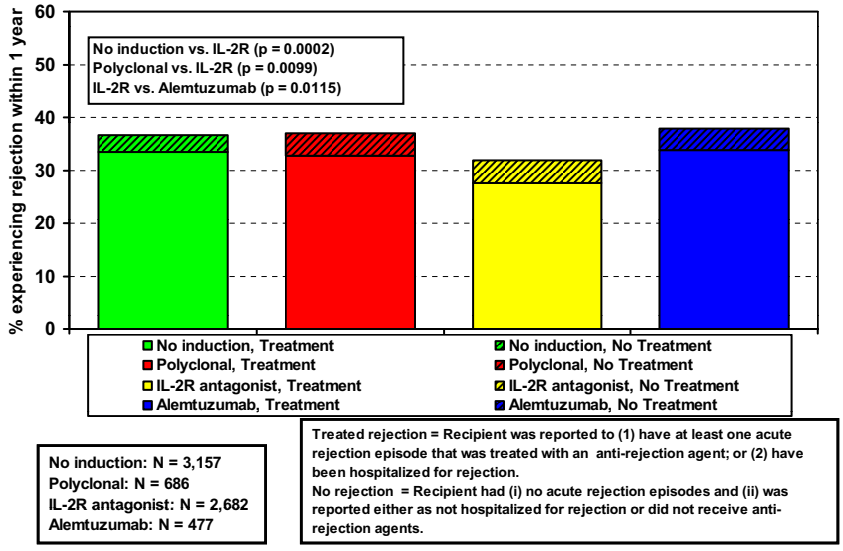

Figure 10 Reported rejection between discharge and the 1-year follow-up for adult lung transplant follow-up assessments from July 2004 through June 2010, stratified by type of induction therapy. Rejection is classified as treated (solid) or untreated (hatched). IL-2R, interleukin-2 receptor. Analysis is limited to patients who were alive at the time of the discharge.

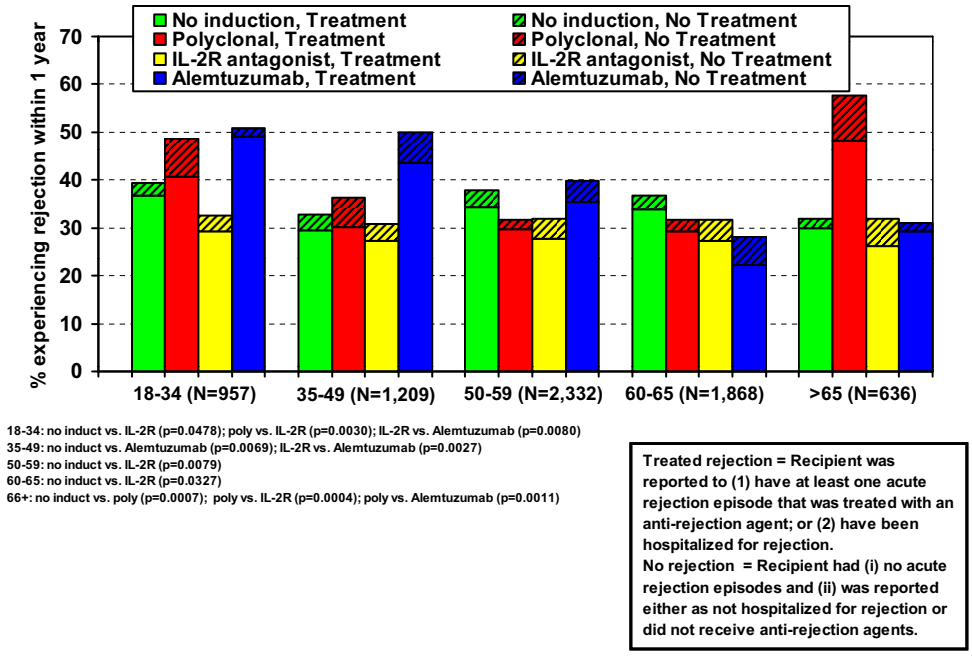

Figure 11 Reported rejection between discharge and 1-year follow-up for adult lung transplant follow-ups from July 2004 through June 2010, stratified by type of induction therapy and age. Rejection is classified as treated (solid) or untreated (hatched). IL-2R, interleukin-2 receptor. Analysis is limited to patients who were alive at the time of the discharge.

worse short-term and long-term survival: the survival half-life for patients aged older than 65 was 3.5 years compared with 6.7 years for those aged 35 to 49. These differences seem to be the effect of worse longer-term survival in the older age groups: 1-year survival was 75% in recipients older than 65 compared with 79% to 80% for those younger than 50; whereas 5-year survival was 38% in those older than 65 vs 55% to 57% in those younger than 50. Of note, these age-related survival differences may actually be more prominent after adjustment for era because most of the transplants in older patients occurred during more recent eras, which have better overall reported survival.

Overall survival data stratified by pre-transplantation diagnosis are presented in Figure 17. Unadjusted 3-month mortality after transplantation is highest in idiopathic pulmonary arterial hypertension (IPAH, 24%), sarcoidosis (17%), and idiopathic pulmonary fibrosis (IPF, 15%), and was lowest in COPD (9%), most likely due to differences in early complications such as primary graft dysfunction. However, when these differences in early mortality are accounted for by conditioning on survival to 3 months (available at www.ishlt.org/registries) or to 1 year (Figure 18), these survival trends essentially reverse, with the exception of IPF. In contrast to overall survival rates, half-life survival among patients surviving at least 1 year was significantly better in recipients with CF (10.4 years), IPAH (9.5 years), sarcoidosis (8.0 years), and AAT-deficiency emphysema (8.7 years) than in those with COPD (6.8 years) and IPF (6.9 years).

Survival comparisons within diagnoses, reported by procedure type, recipient age, and era, are presented in supplemental slides available at www.ishlt.org/registries/. Within

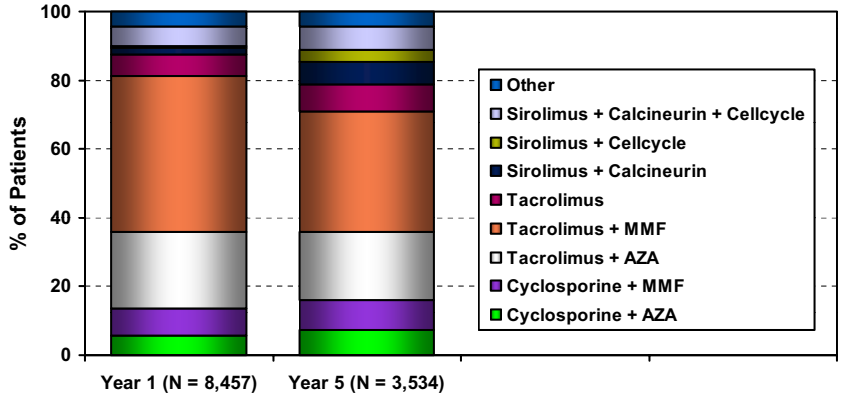

Figure 12 Snapshot of maintenance immunosuppressive drug usage at 1 and 5 years after adult lung transplantation for follow-up assessments between January 2002 and June 2010. Analysis is limited to patients receiving prednisone and who were alive at follow-up. AZA, azathioprine; MMF, mycophenolate mofetil.

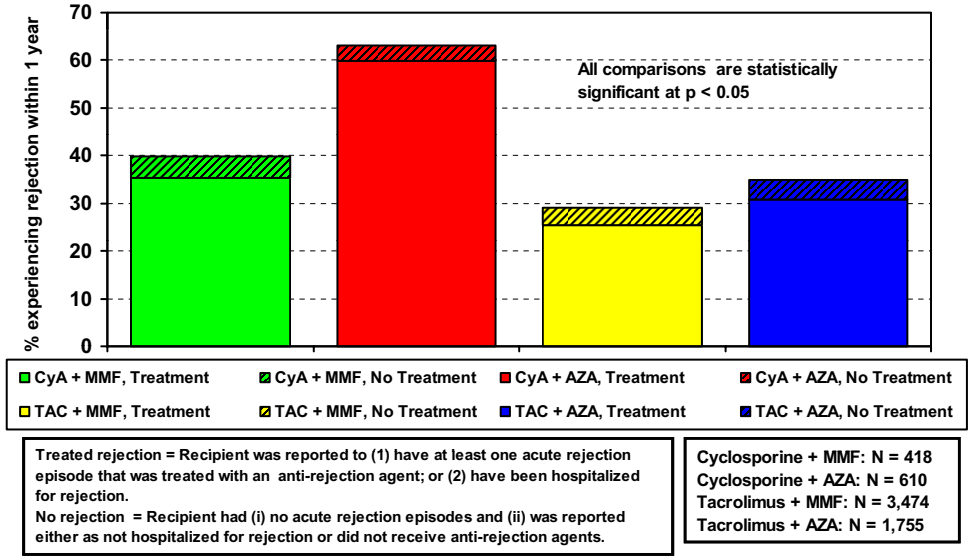

Figure 13 Reported rejection between discharge and 1-year follow-up for adult lung transplant follow-ups from July 2004 through June 2010, stratified by maintenance immunosuppressive regimen. Rejection is classified as treated (solid) or untreated (hatched). AZA, azathioprine; CyA, cyclosporine A; MMF, mycophenolate mofetil; TAC, tacrolimus. Analysis is limited to patients who were alive at the time of the follow-up.

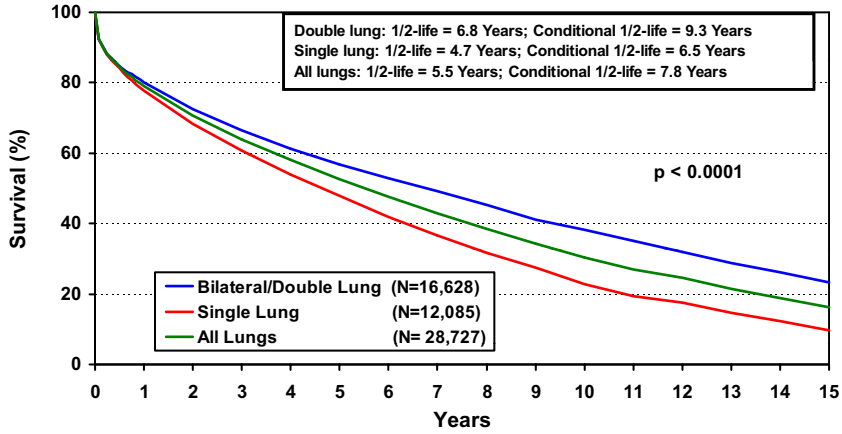

Figure 14 Kaplan-Meier survival by procedure type for adult lung transplants performed between January 1994 and June 2009. Conditional half-life is the time to 50% survival for the recipients who were alive 1 year after transplantation.

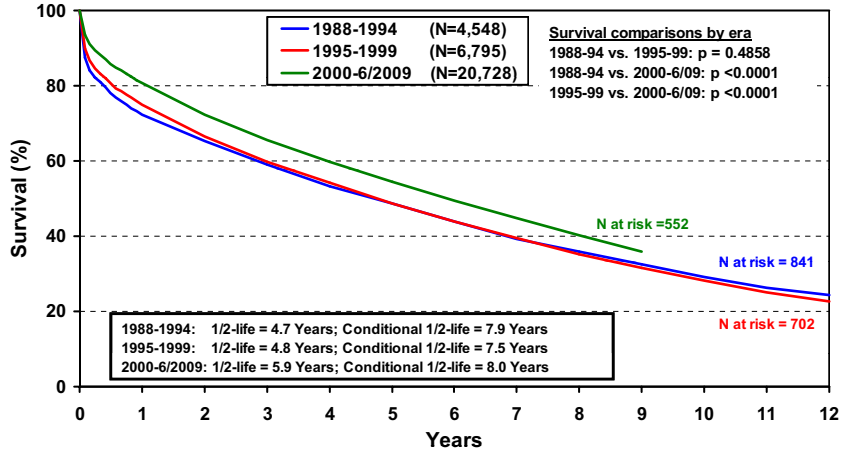

Figure 15 Kaplan-Meier survival by era for adult lung transplants performed between January 1988 and June 2009. Conditional half-life is the time to 50% survival for the recipients who were alive 1 year after transplantation.

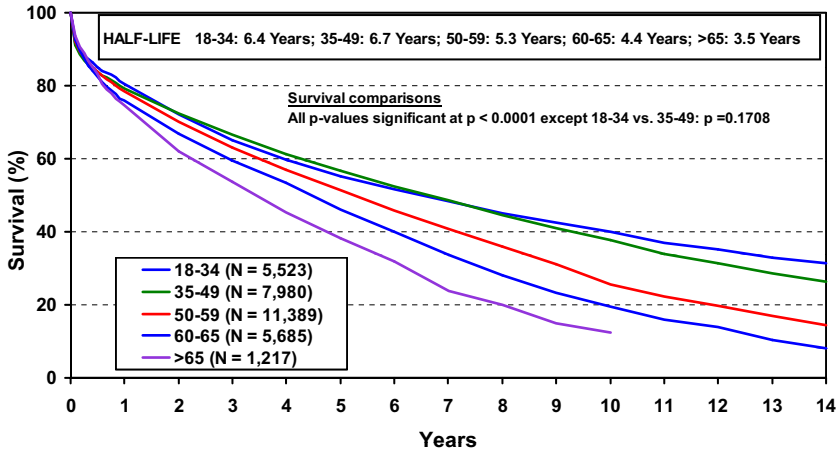

Figure 16 Kaplan-Meier survival by age group for adult lung transplants performed between January 1990 and June 2009.

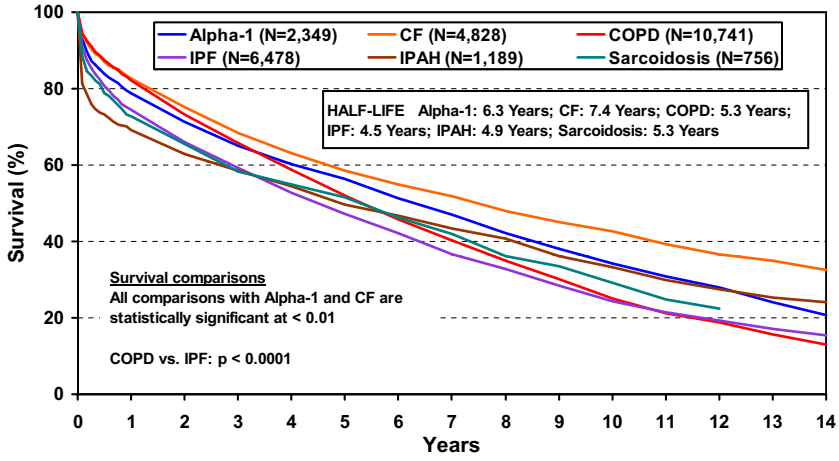

Figure 17 Kaplan-Meier survival by diagnosis for adult lung transplants performed between January 1990 and June 2008. AT Def, α1-antitrypsin–deficiency emphysema; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis.

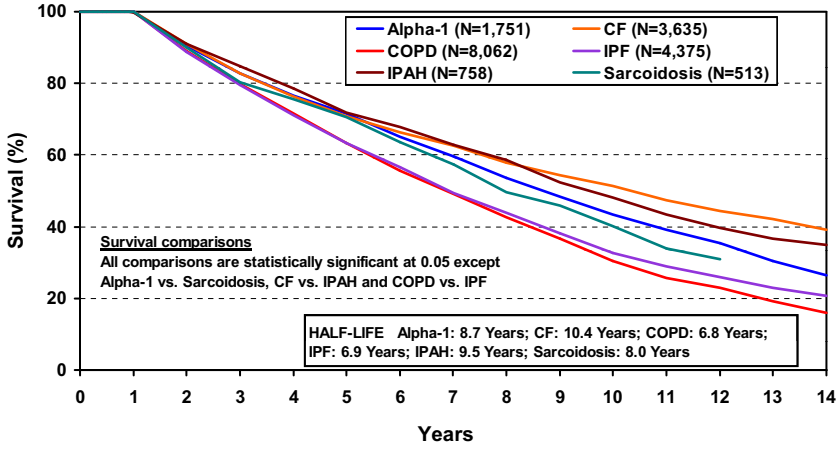

Figure 18 Kaplan-Meier survival by diagnosis for adult lung transplants performed between January 1990 and June 2009, conditioned on surviving to one year. AT Def, α1-antitrypsin–deficiency emphysema; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis.

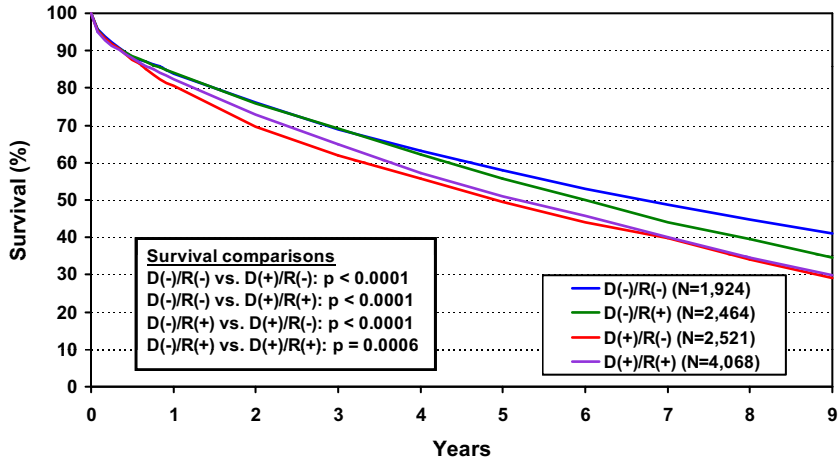

Figure 19 Kaplan-Meier survival by donor-recipient cytomegalovirus serologic status for adult lung transplants performed between October 1999 and June 2009. D, donor; R, recipient.

each diagnosis category, bilateral procedures and more current eras had the appearance of better survival, although these analyses were not adjusted for other covariates and should be interpreted accordingly.

Survival stratified by combinations of donor and recipient pre-transplantation cytomegalovirus (CMV) serologic status is displayed in Figure 19. As reported in prior years, survival appears to be most influenced by the donor's CMV status, with a little better survival reported for donor CMV naïve transplants, regardless of recipient status ($p < 0.001$ for all comparisons). Although the underlying reasons for the association of CMV seropositivity with higher mortality are not known, immunogenic or fibrotic effects of CMV activation in the allograft are potential explanations warranting further investigation.

Causes of death

Causes of death derived from data reported from January 1992 to June 2010 are presented in Table 2. The major reported causes of identifiable mortality are graft failure and non-CMV infections within the first 30 days, and these 2 causes also dominate causes of death during the remainder of the first year. After the first year, the most common causes of identifiable reported mortality were bronchiolitis obliterans syndrome (BOS) and non-CMV infections, given that late deaths coded as "graft failure" are difficult to classify and most likely represent rejection or BOS. Reported deaths due to malignancies increase as time from transplant increases and account for 15% of all deaths between 5 and 10 years after transplant and 16% of reported deaths after 10 years.

Risk factors for death

Risk factors for death at 1 and 5 years were evaluated using multivariable Cox proportional hazards models. Categoric risk factors for 1-year mortality are displayed in Table 3, based on data from transplants performed between January 1997 and June 2009. As in prior reports, the underlying lung disease of the recipient and illness at the time of transplantation (including hospitalization and use of dialysis, ino-

Table 2 Causes of Deaths for Adult Lung Transplant Recipients for Transplants From January 1992 Through June 2010

Cause of death	0–30 days (n = 2,204) No. (%)	31 days–1 year (n = 3,781) No. (%)	>1–3 years (n = 3,425) No. (%)	>3–5 years (n = 1,962) No. (%)	>5–10 years (n = 2,336) No. (%)	>10 years (n = 675) No. (%)
Bronchiolitis	7 (0.3)	180 (4.8)	870 (25.4)	566 (28.8)	572 (24.5)	128 (19.0)
Acute rejection	81 (3.7)	70 (1.9)	55 (1.6)	12 (0.6)	18 (0.8)	5 (0.7)
Lymphoma	1 (0.0)	92 (2.4)	67 (2.0)	36 (1.8)	58 (2.5)	27 (4.0)
Malignancy, other	3 (0.1)	112 (3.0)	226 (6.6)	180 (9.2)	289 (12.4)	78 (11.6)
Infection						
CMV	0	98 (2.6)	32 (0.9)	6 (0.3)	4 (0.2)	1 (0.1)
Non-CMV	442 (20.1)	1,334 (35.3)	786 (22.9)	374 (19.1)	417 (17.9)	120 (17.8)
Graft failure	597 (27.1)	655 (17.3)	660 (19.3)	364 (18.6)	428 (18.3)	111 (16.4)
Cardiovascular	239 (10.8)	168 (4.4)	141 (4.1)	105 (5.4)	122 (5.2)	62 (9.2)
Technical	207 (9.4)	94 (2.5)	22 (0.6)	11 (0.6)	16 (0.7)	9 (1.3)
Other	627 (28.4)	978 (25.9)	566 (16.5)	308 (15.7)	412 (17.6)	134 (19.9)

CMV, cytomegalovirus.

Table 3 Categoric Risk Factors for 1-Year Mortality in Adult Lung Transplant Recipients for Transplants from January 1997 to June 2009 (N = 13,937)

Category and risk factor	No.	RR (95% CI)	p-value
Diagnosis			
IPAH	379	2.06 (1.53–2.77)	<0.0001
Retransplant	481	1.90 (1.53–2.35)	<0.0001
Other[a]	870	1.66 (1.36–2.02)	<0.0001
AAT-single	323	1.57 (1.22–2.01)	0.0004
AAT-double	450	1.36 (1.06–1.75)	0.0172
Sarcoidosis, double	293	1.56 (1.17–2.09)	0.0024
Pulmonary fibrosis (not IPF)	404	1.36 (1.08–1.72)	0.0091
IPF, single	2,013	1.29 (1.08–1.54)	0.0059
IPF, double	1,428	1.26 (1.03–1.54)	0.0242
Cystic fibrosis	1,867	1.16 (0.93–1.46)	0.1941
Lymphangioleiomyomatosis	116)	0.41 (0.18–0.92)	0.0311
Donor			
History of diabetes	560	1.44 (1.21–1.72)	<0.0001
Recipient			
Dialysis	61	2.66 (1.84–3.84)	<0.0001
Intravenous inotropes	49	1.74 (1.16–2.60)	0.0076
Hospitalized (including ICU)	1,513	1.70 (1.50–1.93)	<0.0001
Ventilator support	491	1.57 (1.31–1.88)	<0.0001
Transplant			
Transplant year			
1997/1998 vs 2008/2009	1,625	1.89 (1.61–2.22)	<0.0001
1999/2000 vs 2008/2009	1,656	1.87 (1.60–2.19)	<0.0001
2001/2002 vs 2008/2009	2,023	1.51 (1.29–1.76)	<0.0001
2005/2006 vs 2008/2009	2,764	1.18 (1.03–1.36)	0.0177
2007 vs 2008/2009	1,418	1.18 (1.01–1.38)	0.0425
2003/2004 vs 2008/2009	2,187	1.17 (1.01–1.37)	0.0424
Donor CMV+/recipient CMV–	2,887	1.21 (1.10–1.32)	<0.0001

AAT, α1-antitrypsin deficiency; CI, confidence interval; CMV, cytomegalovirus; ICU, intensive care unit; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; RR, relative risk.

Reference group = chronic obstructive pulmonary disease/emphysema, single lung.

[a]All diagnoses other than chronic obstructive pulmonary disease; idiopathic pulmonary arterial hypertension, IPF, cystic fibrosis, pulmonary fibrosis, bronchiectasis, ATT deficiency, retransplant and lymphangioleiomyomatosis.

tropes, and mechanical ventilation) are key determinants of the risk of death during the first year. Diagnosis categoric variables were evaluated for effect modification by transplant procedure type, and several diagnosis categories are therefore presented separately for single and bilateral procedures. Compared with the most common group used as a reference (single-lung COPD), most indications for transplant have an increased mortality risk, including approximately 2-fold increases in 1-year mortality risk for IPAH and retransplantation.

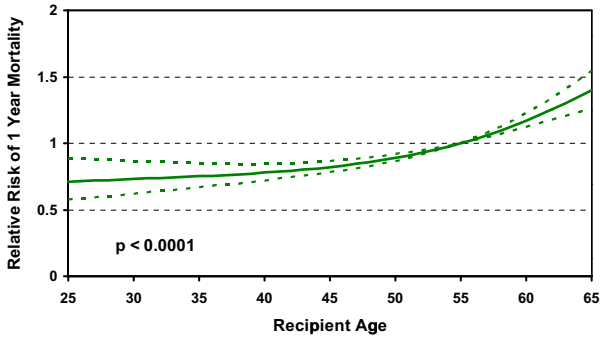

Figure 20 Association of recipient age with the relative risk of death within 1 year after transplantation for adult lung transplants performed between January 1996 and June 2009. The dotted lines indicate the 95% confidence interval.

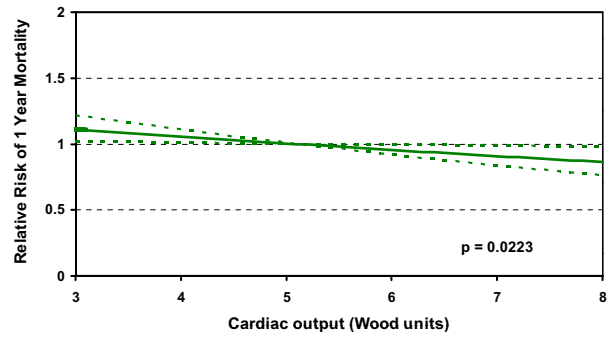

Figure 21 Association of pre-transplant cardiac output with the relative risk of death within 1 year after transplantation for adult lung transplants performed between January 1996 and June 2009. The dotted lines indicate the 95% confidence interval.

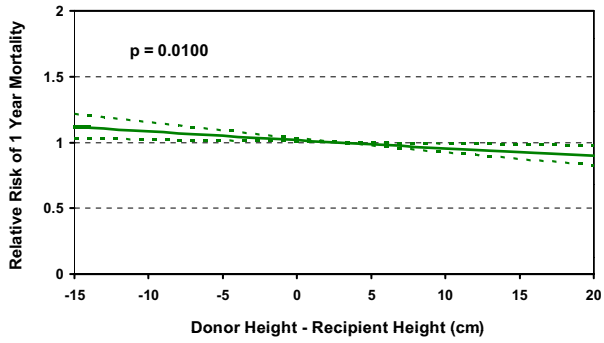

Figure 22 Association of pre-transplant donor-recipient height difference with the relative risk of death within 1 year after transplantation for adult lung transplants performed between January 1996 and June 2009. A positive value represents a larger donor height than recipient height. The dotted lines indicate the 95% confidence interval.

Continuous variables with significant adjusted associations with 1-year mortality included older recipient age (Figure 20), higher pre-transplant bilirubin level, higher supplemental oxygen requirement at rest, lower cardiac output (Figure 21), lower transplant center volume, lower forced vital capacity, and more negative donor-recipient height difference (Figure 22). Analyses of differences in donor and recipient heights imply that recipients with larger donors seem to do better. However, this finding may have been affected by residual uncontrolled confounding by diagnosis category, because COPD recipients usually have larger donors (more positive differences), and IPF patients have smaller donors (more negative differences). This theory is supported by the relationship of lower forced vital capacity and mortality. The relationships of lower cardiac output and higher bilirubin may be markers of right heart failure. Graphic depictions of these relationships, with mortality for all significant continuous variables, are available at www.ishlt.org/registries/. Analyses of 1-year mortality performed within the diagnosis category yielded similar risk factor results, for the most part, to those categoric and continuous variables reported above (available at www.ishlt.org/registries/).

Categoric risk factors for 5-year mortality are presented in Table 4, with survival results conditional on 1-year survival presented in Table 5. As in prior reports, there are differences between overall and conditional survival for diagnosis categories, consistent with differential contributions of early and late mortality. Recipient characteristics also differ between overall and conditional survival analyses, with chronic diseases (such as diabetes) having larger effects on longer-term mortality. As in prior reports, post-transplant complications, including BOS, acute rejection, and drug-treated infection are significant risk factors conditional on surviving 1 year (Table 5).

Figures for significant continuous risk factors for overall and conditional 1-year mortality are available at www.ishlt.org/registries/. Factors significantly associated with risk of 5-year mortality are similar to those for 1-year mortality. Significant risk factors for 5-year mortality conditional on surviving 1 year again included low and higher recipient age as well as lower transplant center volume

Table 4 Categoric Risk Factors for 5-Year Mortality in Adult Lung Transplant Recipients for Transplants from January 1997 Through June 2005 (N = 8,163)

Category and risk factor	No.	RR (95% CI)	p-value
Diagnosis			
Retransplant	204	1.25 (1.01–1.55)	0.0380
COPD/emphysema, double	979	0.87 (0.78–0.98)	0.0238
Cystic fibrosis	1,163	0.77 (0.64–0.93)	0.0075
Lymphangioleiomyomatosis	71	0.51 (0.32–0.82)	0.0052
Donor			
History of diabetes	238	1.35 (1.13–1.61)	0.0011
Cause of death = anoxia	468	0.79 (0.68–0.92)	0.0020
Recipient			
Receiving dialysis	21	2.18 (1.33–3.59)	0.0020
Intravenous inotropes	47	2.09 (1.46–3.00)	<0.0001
Hospitalized (including ICU)	612	1.30 (1.13–1.49)	0.0002
Prior sternotomy	319	1.25 (1.08–1.46)	0.0035
History of diabetes	717	1.20 (1.06–1.34)	0.0025
Chronic steroid use	3,864	1.11 (1.04–1.19)	0.0018
Transplant			
Transplant year			
1997/1998 vs 2003–2005	1,625	1.34 (1.22–1.47)	<0.0001
1999/2000 vs 2003–2005	1,656	1.28 (1.17–1.40)	<0.0001
Donor CMV +/recipient CMV–	1,544	1.14 (1.06–1.24)	0.0011

CI, confidence interval; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; RR, relative risk.

Reference group = COPD/emphysema, single lung.

Table 5 Categoric Risk Factors for 5-Year Mortality Conditional on Survival to 1 Year in Adult Lung Transplant Recipients for Transplants from January 1997 Through June 2005 (N = 6,305)

Category and risk factor	No.	RR (95% CI)	p-value
Diagnosis			
COPD/emphysema, double	796	0.82 (0.71–0.96)	0.0158
Idiopathic pulmonary fibrosis, double	362	0.67 (0.52–0.87)	0.0023
α-1 antitrypsin deficiency, double	254	0.65 (0.50–0.86)	0.0021
Cystic fibrosis	959	0.59 (0.45–0.76)	<0.0001
Idiopathic pulmonary arterial hypertension	202	0.51 (0.34–0.77)	0.0011
Lymphangioleiomyomatosis	63	0.48 (0.27–0.84)	0.0103
Other,[a] single	90	0.46 (0.29–0.74)	0.0011
Donor			
Cause of death = anoxia	373	0.73 (0.59–0.90)	0.0030
Recipient			
Prior sternotomy	227	1.33 (1.08–1.64)	0.0076
Hospitalized (including intensive care unit)	397	1.29 (1.07–1.55)	0.0082
History of diabetes	540	1.27 (1.09–1.48)	0.0025
Chronic steroid use	2,944	1.10 (1.00–1.20)	0.0420
Ventilator support	95	0.57 (0.37–0.88)	0.0106
Transplant			
Mismatches at HLA A locus, per mismatch		1.16 (1.01–1.34)	0.0389
0A	393		
1A	3,216		
2A	2,696		
D CMV+/R CMV −	1,175	1.15 (1.04–1.28)	0.0090
Male D/female R vs male D/male R	1,283	1.15 (1.01–1.30)	0.0311
Post-transplant			
OB within 1 year after transplant	415	2.18 (1.90–2.51)	<0.0001
Post-transplant dialysis before discharge	159	1.31 (1.01–1.70)	0.0389
Rejection between discharge and 1 year	2,859	1.18 (1.08–1.29)	0.0003
Treated for infection by discharge	2,511	1.12 (1.02–1.22)	0.0132

CI, confidence interval; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; D, donor; HLA, human leukocyte antigen; OB, obliterative bronchiolitis; R, recipient; RR relative risk.

Reference group = COPD/Emphysema, Single lung.

[a]Other = All diagnoses other than COPD, idiopathic pulmonary arterial hypertension, idiopathic pulmonary fibrosis, cystic fibrosis, pulmonary fibrosis, bronchiectasis, α-1 antitrypsin deficiency, retransplant, and lymphangioleiomyomatosis.

(Figure 23). The effects of transplant center volume seem to be most prominent for centers performing fewer than approximately 20 procedures per year. These findings indicate that programmatic differences exist that influence longer-term survival among centers beyond those factors specific to the transplant.

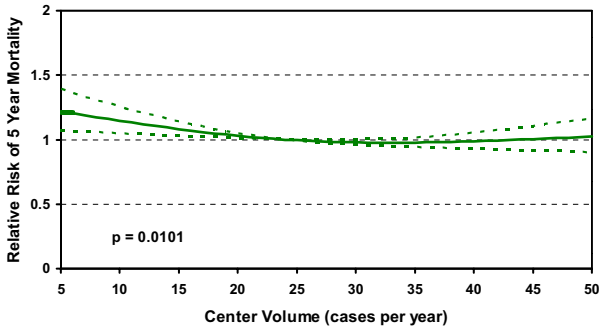

Figure 23 Association of center volume with the relative risk of death within 5 year after transplantation conditional on 1-year survival for adult lung transplants performed between January 1996 and June 2005. The dotted line shows the 95% confidence interval.

Complications and morbidities

Table 6 details common morbidities reported among 1-year and 5-year survivors. As in past reports, morbidities present at 5 years are those commonly caused or exacerbated by immunosuppressive medicines, including hypertension, renal dysfunction, diabetes, and dyslipidemia. Within 5 years of transplant, 2.5% of those with follow-up data report long-term dialysis, and this number reaches 6.5% within 10 years among those with follow-up data (data available at www.ishlt.org/registries/). As in prior reports, BOS remains common, conditioned on surviving 2 weeks to avoid biases introduced by early death (Figure 24). BOS was reported in 49% of recipients by 5 years after transplantation and in 75% by 10 years, on the basis of data reported between April 1994 and June 2010, including more than 13,000 recipients who survived at least 14 days. These data are essentially unchanged from recent Registry reports, indicat-

Table 6 Morbidity after Adult Lung Transplantation in Surviving Recipients for Follow-up From April 1994 Through June 2010

Outcome	≤ 1 year (%)	Total with known response (No)	≤ 5 years (%)	Total with known response (No.)
Hypertension	52.3	12,858	83.7	3,678
Renal dysfunction	23.9	14,130	33.3	4,439
Abnormal creatinine < 2.5 mg/dl	16.6		22.7	
Creatinine > 2.5 mg/dl	5.6		7.7	
Chronic Dialysis	1.6		2.5	
Renal Transplant	0.1		0.4	
Hyperlipidemia	24.7	13,574	57.5	4,012
Diabetes	26.2	14,074	39.6	4,137
Bronchiolitis obliterans syndrome	9.5	13,280	37.9	3,487

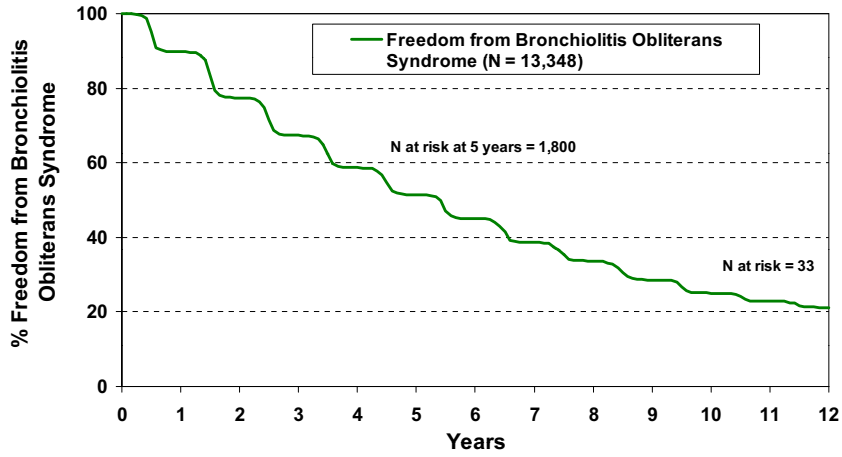

Figure 24 Freedom from bronchiolitis obliterans syndrome in adult lung recipients for follow-up assessments between April 1994 and June 2010, conditional on survival to 14 days.

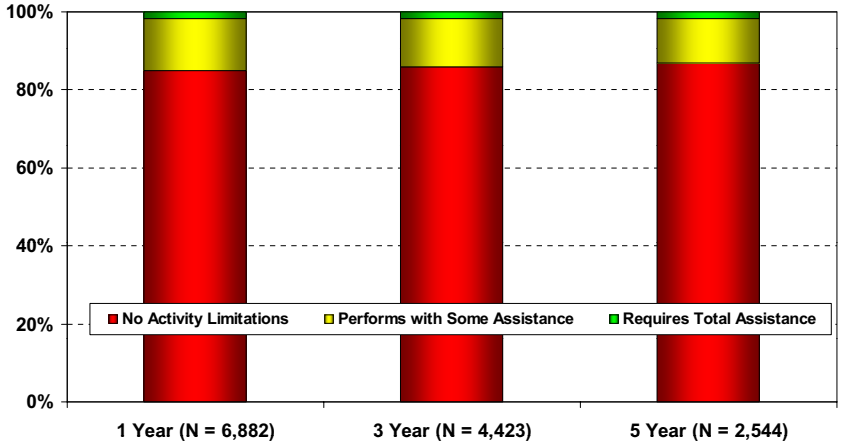

Figure 25 Cross sectional analysis of functional status reported at 1, 3, and 5 years after adult lung transplantation for follow-up assessments between April 1994 and June 2010.

Table 7 Malignancy after Adult Lung Transplantation in Surviving Recipients for Follow-up From April 1994 Through June 2010

	Survivors, No. (%)		
Malignancy/Type	1 year	5 years	10 years
No malignancy	14,023 (96.5)	3,925 (86.8)	571 (72.6)
Malignancy (all types combined)	513 (3.5)	597 (13.2)	216 (27.4)
Malignancy type[a]			
Skin	149	378	143
Lymph	212	72	34
Other	131	169	65
Type not reported	21	9	0

[a]Recipients may have had more than one type of malignancy, so the sum of the individual types can exceed the total number of recipients with malignancy.

ing the unchanged importance of BOS as a long-term morbidity. Furthermore, freedom from BOS does not appear to vary much according to age group or major diagnosis category (data available at www.ishlt.org/registries/).

Although reporting of functional status is not universally complete in the Registry and thus may be affected by missing data, more than 80% of surviving patients have no reported activity limitations at 1, 3, and 5 years (Figure 25). Other outcomes data on functional status, employment, and rehospitalization rates can be found in supplemental slides at www.ishlt.org/registries/.

Malignancies are common after lung transplantation: 13% of surviving recipients reported at least 1 malignancy at 5 years after transplantation and 27% at 10 years after transplantation (Table 7). As intervals from the time of transplantation increase, the major types of reported malignancy shift from lymphoma to skin and other cancers.

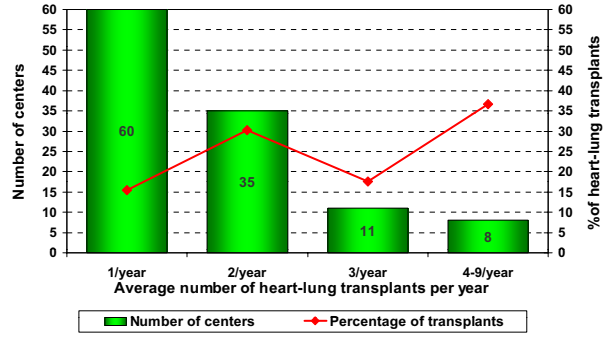

Figure 27 Distribution of heart-lung transplants by center volume, January 1998 through June 2010. The bars indicate number of centers and the line graph indicates percentage of total transplants by center volume.

Heart-lung transplantation

Centers and activity

Participating centers reported 87 adult and pediatric heart-lung transplants to the Registry for calendar year 2009 (Figure 26). The number of heart-lung transplant procedures has been essentially similar since 2003: 87 to 114 transplants are reported each year. Of note, these numbers are somewhat higher than prior years due to the new addition of data from centers not previously reporting to the Registry. Between January 1998 and June 2010, 46% of the heart-lung transplant procedures were performed at 95 centers averaging only 1 or 2 heart-lung transplants per year (Figure 27), whereas 37% of procedures were performed at the 8 centers averaging between 4 and 9 reported procedures per year.

Indications and demographics

Congenital heart disease, PAH, and CF remain the main indications for adult heart-lung transplantation (Table 8).

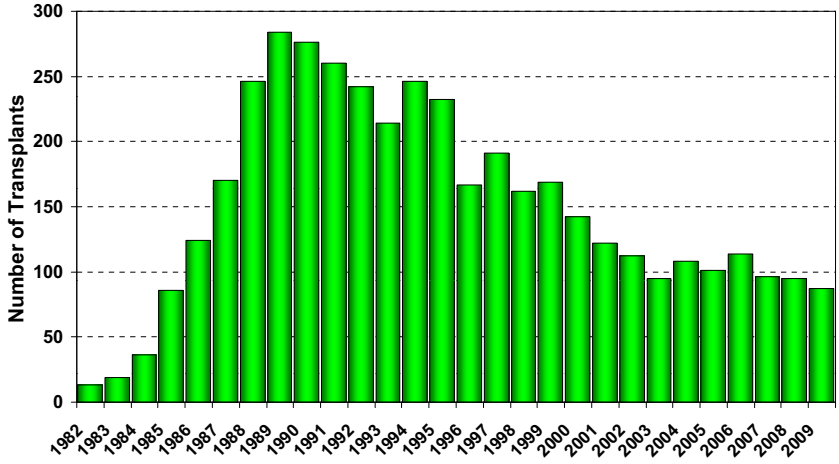

Figure 26 Number of heart-lung transplants reported by year. This figure includes transplants transmitted to the International Society for Heart and Lung Transplantation (ISHLT) Registry from organ exchange organizations in countries with a data-sharing agreement and transplants reported by individual centers in countries without a specific data-sharing agreement between ISHLT and the national transplant organization. Therefore, this figure may not fully represent the total number of procedures worldwide.

Table 8 Distribution of Diagnoses Among Adult Heart-Lung Transplant Recipients for Transplants From January 1982 Through June 2010

Diagnosis	No. (%)
Congenital heart disease	1,116 (35.9)
Idiopathic pulmonary arterial hypertension	857 (27.5)
Cystic fibrosis	444 (14.3)
Acquired heart disease	150 (4.8)
COPD/emphysema	132 (4.2)
Idiopathic pulmonary fibrosis	113 (3.6)
α-1 antitrypsin deficiency	60 (1.9)
Sarcoidosis	50 (1.6)
Retransplant:	
Not obliterative bronchiolitis	36 (1.2)
Obliterative bronchiolitis	28 (0.9)
Bronchiectasis	24 (0.8)
Obliterative bronchiolitis (not retransplant)	22 (0.7)
Other	80 (2.6)

COPD, chronic obstructive pulmonary disease.

During the past 2 decades, the proportions of transplants for diagnoses of congenital heart disease and PAH have increased, whereas the proportion of heart lung transplant for CF has decreased (Figure 28). However, between January 2000 and June 2010, a greater proportion of procedures at North American centers were performed for congenital heart disease, whereas European and other non-North American centers performed a greater proportion of transplants for CF (Figure 29).

Immunosuppression

Figure 30 displays trends in induction therapy during the past decade. The use of induction therapy is generally more common in heart-lung transplant recipients than in lung transplant recipients, with between 62% and 83% of recipients receiving induction therapy during the last 4 years. During the past decade, IL-2R antagonists have been more commonly administered, whereas the use of anti-lymphocyte globulins and OKT3 has decreased.

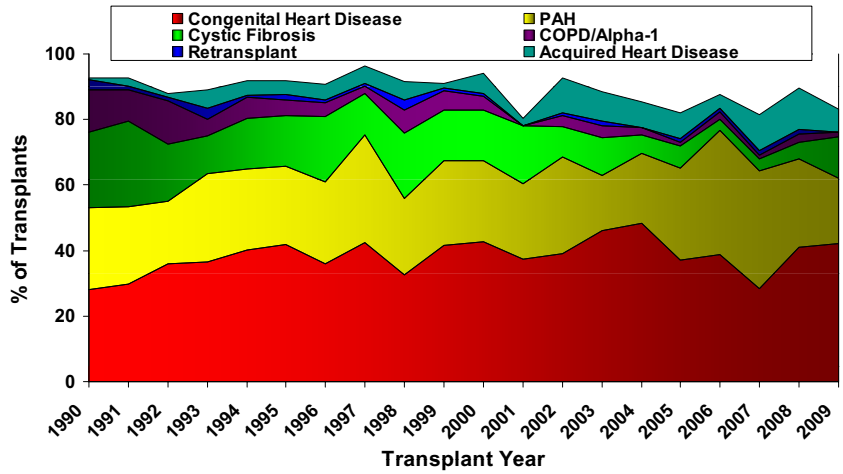

Figure 28 Indications for adult heart-lung transplants by year for transplantations from January 1982 through December 2009. Alpha, α1-antitrypsin–deficiency emphysema; COPD, chronic obstructive pulmonary disease; PAH, pulmonary arterial hypertension.

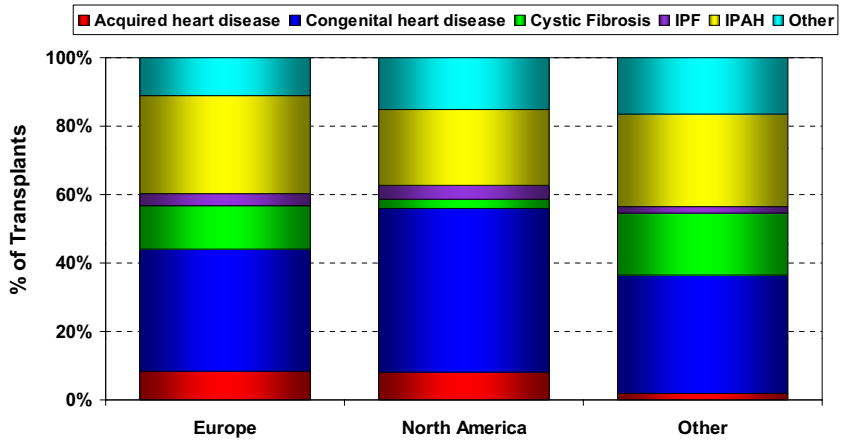

Figure 29 Diagnosis distribution by location for transplants performed between January 2000 and June 2010. IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis.

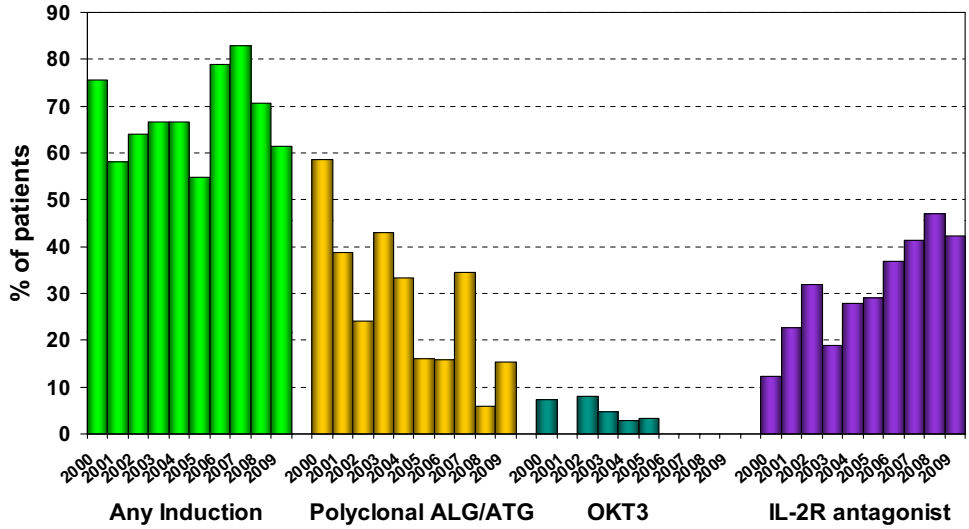

Figure 30 Induction immunosuppression by year in adult heart-lung recipients for transplants between January 2000 and December 2009. ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; IL-2R, interleukin-2 receptor. Analysis is limited to patients who were alive at the time of the discharge.

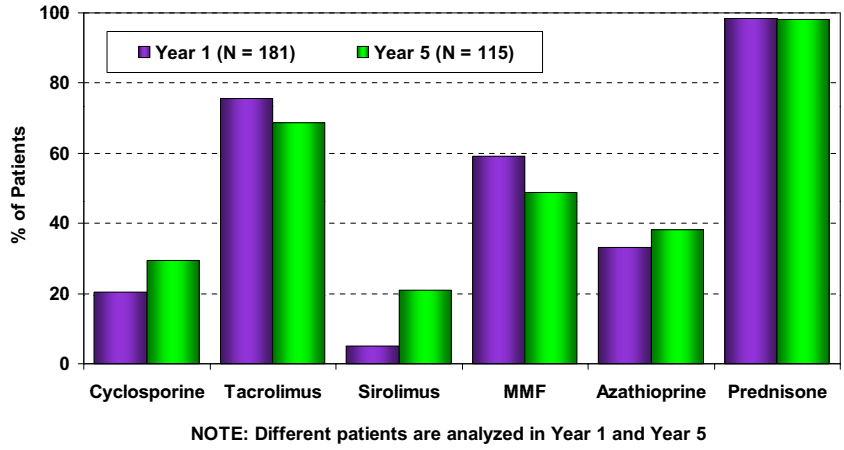

Figure 31 Snapshot of maintenance immunosuppressive drug usage at 1 and 5 years after adult heart-lung transplantation for follow-up assessments between January 2001 and June 2010. MMF, mycophenolate mofetil. Analysis is limited to patients who were alive at the time of the discharge.

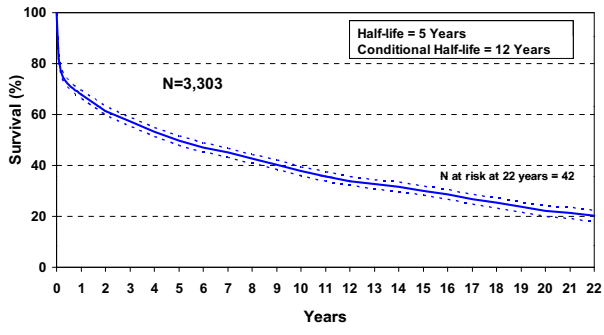

Figure 32 Kaplan-Meier survival for adult heart-lung transplants performed between January 1982 and June 2009. The dashed lines indicate 95% confidence intervals. Conditional half-life is the time to 50% survival for recipients who were alive 1 year after transplantation.

Figure 31 shows snapshot maintenance immunosuppressive protocols at 1 and 5 years after transplantation. As in lung transplant analyses, these data do not represent the same patients in the 2 time period groups. The most common regimens included tacrolimus (76% at 1 year, and 69% at 5 years), mycophenolate (59% and 49%), and prednisone (nearly uniform) at both intervals. The use of sirolimus increased from 5% at 1 year to 21% at the 5 years after transplant.

Survival

Figure 32 presents overall survival for 3,303 heart-lung transplants performed between January 1982 and June 2009. Most deaths after heart-lung transplantation occur in the first year, with survival rates of 75% at 3 months and

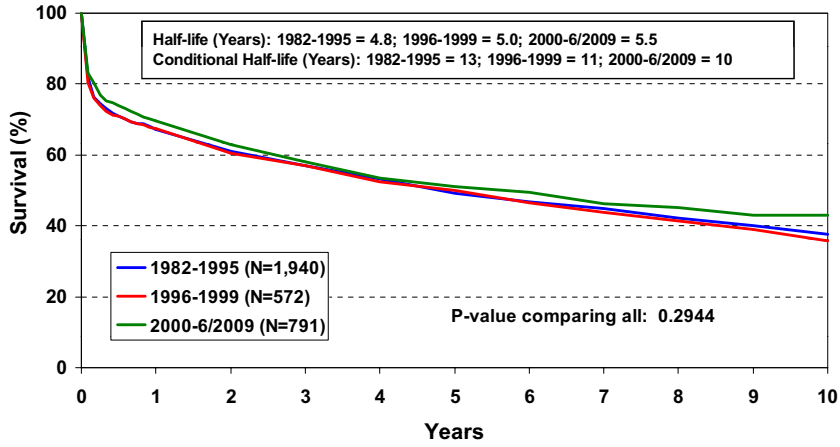

Figure 33 Kaplan-Meier survival by era for adult heart-lung transplants performed between January 1982 and June 2009. Conditional half-life is the time to 50% survival for the sub-set of recipients who were alive 1 year after transplantation.

Table 9 Causes of Death after Heart-Lung Transplantation in Adult Recipients for Deaths From January 1992 Through June 2010

Cause of death	0-30 days (n = 321) No. (%)	31 days–1 year (n = 249) No. (%)	>1–3 years (n = 223) No. (%)	>3–5 years (n = 151) No. (%)	>5 years (n = 391) No. (%)
Bronchiolitis	0	6 (2.4)	50 (22.4)	32 (21.2)	66 (16.9)
Acute rejection	3 (0.9)	8 (3.2)	4 (1.8)	1 (0.7)	2 (0.5)
Lymphoma	0	8 (3.2)	11 (4.9)	8 (5.3)	11 (2.8)
Malignancy, other	0	4 (1.6)	12 (5.4)	5 (3.3)	30 (7.7)
Infection					
CMV	0	1 (0.4)	0	1 (0.7)	1 (0.3)
Non-CMV	52 (16.2)	80 (32.1)	67 (30.0)	42 (27.8)	96 (24.6)
Graft failure	92 (28.7)	54 (21.7)	34 (15.2)	27 (17.9)	54 (13.8)
Cardiovascular	25 (7.8)	11 (4.4)	20 (9.0)	13 (8.6)	45 (11.5)
Technical	71 (22.1)	9 (3.6)	2 (0.9)	1 (0.7)	3 (0.8)
Other	78 (24.3)	68 (27.3)	23 (10.3)	21 (13.9)	83 (21.2)

CMV, cytomegalovirus.

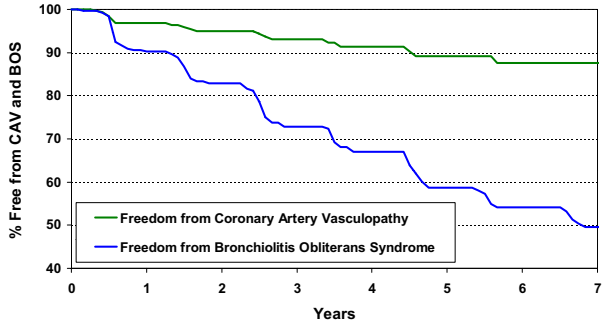

Figure 34 Freedom from coronary artery vasculopathy (CAV) and bronchiolitis obliterans syndrome (BOS) in adult heart-lung recipients for follow-up assessments between April 1994 and June 2010.

68% at 1 year. However, patients who survive the first year have generally good outcomes, with a half-life of 12 years conditional on surviving at least 1 year.

As shown in Figure 33, in contrast to the last year's report, survival no longer shows improvement with each successive era between 1982 and June 2009. Although the overall half-life has improved from 4.8 to 5.5 years in the most recent era, survival conditional on 1-year survival has decreased with more modern eras. These findings (Figure 33) indicate that slight improvements in early mortality rates in more recent eras have been offset by slightly worse longer-term outcomes, perhaps due to differences in age or diagnoses in more modern eras. Again, survival differed according to pre-transplantation diagnosis, with Eisenmenger syndrome having the best overall and conditional survival among the most common indications for heart-lung transplantation (see supplemental slides at www.ishlt.org/registries/).

Causes of death

Causes of death after heart-lung transplantation reported between January 1992 and June 2010 are reported in Table 9. Again this year, the most common identifiable causes of death in the first 30 days were graft failure, technical complications, and non-CMV infections. Non-CMV infections and BOS (including late graft failure) were the most common causes of death after the first year. Although increasing

Table 10 Morbidity after Heart-Lung Transplantation in Surviving Adult Recipients for Follow-up from April 1994 Through June 2010

Outcome	≤ 1 year (%)	Total with known response (No.)	≤5 years (%)	Total with known response (No.)
Hypertension	58.5	386	87.6	137
Renal dysfunction	18.4	412	26.3	160
Abnormal creatinine < 2.5 mg/dl	12.1		18.8	
Creatinine > 2.5 mg/dl	2.9		6.3	
Chronic dialysis	3.2		1.3	
Renal transplant	0.2		0.0	
Hyperlipidemia	26.4	406	68.8	144
Diabetes	19.1	414	26.1	153
Coronary artery vasculopathy	3.1	327	7.2	83
Bronchiolitis obliterans syndrome	8.5	388	27.9	129

over time, cardiovascular causes of death were relatively less common, as in last year's report.

Complications and morbidities

Figure 34 presents freedom from BOS and coronary artery vasculopathy among recipients who survived at least 14 days. At all time points, BOS was more commonly reported than coronary artery vasculopathy. By 5 years, 59% of heart-lung transplant recipients were BOS-free, conditional on survival to 14 days, compared with 89% reported as free of coronary artery vasculopathy, conditional on 14-day survival.

Table 10 lists other morbidities among 1-year and 5-year survivors of adult heart-lung transplantation. Similar to lung transplant patients, side effects of immunosuppressive therapy were common, including systemic hypertension and hyperlipidemia as the most commonly reported morbidities at the 1-year and 5-year intervals after heart-lung transplantation. The proportion of surviving patients reporting malignancies at 1, 5, and 10 years is presented in Table 11. Similar to last year's report, lymphoma was the most common malignancy, with most reported in the first year.

Table 11 Malignancy After Adult Heart-Lung Transplantation in Surviving Recipients for Follow-up From April 1994 through June 2009

	Survivors, No. (%)		
Malignancy/type	1 year	5 years	10 years
No malignancy	394 (93.8)	143 (88.8)	43 (86)
Malignancy (all types combined)	26 (6.2)	18 (11.2)	7 (14)
Malignancy type[a]			
Skin	2	5	7
Lymph	18	6	0
Other	4	5	0
Type not reported	2	2	0

[a]Recipients may have had more than one type of malignancy, so the sum of the individual types can exceed the total number of recipients with malignancy.

Disclosures

Disclosures All relevant disclosures for the Registry Director, Executive Committee Members and authors are on file with the ISHLT and can be made available for review by contacting the Executive Director of the ISHLT.

All of the figures and tables from this report, and a more comprehensive set of Registry slides are available at www.ishlt.org/registries/

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